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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING

OCTOBER 29, 1984

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RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING[1]

OCTOBER 29, 1984

The Recombinant DNA Advisory Committee (RAC) was convened for its thirty first meeting at 9:00 a.m. on October 29, 1984, in Building 31, Conference Room 10, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20205. Mr. Robert Mitchell (Chair), Attorney at Law in California, presided. In accordance with Public Law 92-463, the meeting was open to the public. The following were present for all or part of the meeting:

Committee members:

Barbara Bowman	Arthur Landy	Fred Rapp
Royston Clowes	Myron Levine	Mark Saginor
L. Albert Daloz	Gerard McGarrity	John Scandalios
David Friedman	John McGonigle	Frances Sharples
Susan Gottesman	Robert McKinney	LeRoy Walters
John Harvin	Mark Mills	Pieter Wensink
King Holmes	Robert Mitchell	Anne Witherby
Wolfgang Joklik	Thomas Pirone	William J. Gartland, Jr. (Executive Secretary)

A committee roster is attached (Attachment I).

Ad hoc consultants:

George Lacy, Virginia Polytechnic Institute State University
David Pimentel, Cornell University

[1]The RAC is advisory to the NIH, and its recommendations should not be considered as final or accepted. NIH action on two of these recommendations was published in the Federal Register on March 11, 1985 (50 FR 9760). The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

Non-voting members:

William Beisel, Department of Defense
Bernadine Bulkley, Office of Science and Technology Policy
John Cox, Department of Commerce
John Fowle, Environmental Protection Agency
Richard Green, Veterans Administration
Stanley Haimes, Department of Labor
Morris Levin, Environmental Protection Agency
Herman Lewis, National Science Foundation
Henry Miller, Food and Drug Administration
Sue Tolin, Department of Agriculture
William Walsh, Department of State

National Institutes of Health staff:

W. French Anderson, NHLBI
Stanley Barban, NIAID
Roy A. Barrett, OD
Fred Bergmann, NIGMS
B. K. Chopra, OD
Thomas Cloutier, OD
Becky Connors, NIAID
Irene Eckstrand, NIGMS
Michael Goldberg, OD
Anne Houser, OD
Elke Jordan, NIGMS
Tejinder Kochhar, OD
Rachel Levinson, OD
Sister Mary Carl Malmstrom, OD
Edward Max, NIAID
Charles McCarthy, OD
Michael E. McClure, NICHD
Elizabeth Milewski, NIAID
Sister Nivard Neft, OD
Alice Settle, NIA
Clauszell Smith, OD
Don Ralbovsky, OD
Bernard Talbot, NIAID
Wayne Wray, OD

Other:

Stanley Abramson, Environmental Protection Agency
Benjamin J. Barnhart, Department of Energy
Fred Betz, Environmental Protection Agency
Mark Bowden, Philadelphia Inquirer
Irene Brandt, Eli Lilly and Company
L. Brown, NBC
Steven Budiansky, Nature Magazine
William L. Chaffee, Miles Laboratories, Inc.

Jeff Christy, Blue Sheet, FDC Reports, Inc.
Judy Curry, Department of Agriculture
Mary Ellen Curtin
Isabelle R. Davidson, Pfizer, Inc.
Richard Denison, Office of Technology Assessment, U.S. Congress
Allen J. Dines, Cetus Madison Corporation
Linda S. Dujack, Hoffmann-La Roche, Inc.
Charles Eby, Monsanto Company
Gershon Fishbein, Environews, Inc.
Diane O. Fleming, Johns Hopkins Institutions
Michael Fox, Humane Society of the United States
Robert J. Frederick, Environmental Protection Agency
Phyllis Freeman, House of Representatives
David Glass, BioTechnica International, Inc.
Carol Lax Gronbeck, Genentech, Inc.
Robert Hager, NBC
Judy Hautala, Genex Corporation
Harold W. Hawk, Department of Agriculture
Joseph Van Houton, Schering-Plough Corporation
Kathleen Henderson, Miles Laboratories, Inc.
Ann Hollander, Environmental Protection Agency
Stephen Humphreys, Bureau of National Affairs, Inc.
Alice K. Jameson, Genencor, Inc.
Susan Jenks, Washington Times
Dorothy Jessop, Department of Agriculture
Janice Johnson, Trends Publishing
Mary Jane Johnson, Pall Corporation
Daniel Jones, Department of Agriculture
James Jones, National Institute for Occupational Safety and Health
Chris Joyce, New Scientist Magazine
Attila Kadar, Food and Drug Administration
Geoffrey Karny, Finnegan, Henderson, Farabow, Garrett, and Dunner
John Keene, Abbott Laboratories
Edgar L. Kendrick, Department of Agriculture
Lorraine Kershner, Office of Assistant Secretary for Health, HHS
Arthur Khusner, Bio/Technology
John Kopchick, Merck Sharp & Dohme Research Laboratories
Lee Koromiskis, MacNeil/Lehrer
Robert Lanman, Office of General Counsel, HHS
Warren Leary, Associated Press
Dan Liberman, Massachusetts Institute of Technology
Kathryn Mahaffey, National Institute for Occupational Safety and Health
Max Marsh, Eli Lilly & Company
Roy D. Meredith, Memel, Jacobs, Pierno & Gersch
Pauline Milius, Department of Justice
Julie Miller, Science News
Kurt Miller, Department of Agriculture
Charles Morin, Burditt, Bowles, & Radzius, Ltd.
Gary Noble, Centers for Disease Control
Elliott A. Norse, Ecological Society of America
Kevin W. O'Connor, Federation of American Societies for Experimental Biology

James Parmentier, University of South Alabama
Richard A. Pelroy, Battelle
Elizabeth Peterson, Department of Justice
Stephen Pijar, Food and Drug Adminstration
Richard Pollock, Richard Pollock Associates, Inc.
Harvey Price, Industrial Biotechnology Association
Frank G. Pugliese, Food and Drug Adminstration
Vernon G. Pursel, Department of Agriculture
Roberta C. Reuben, Merck Sharp & Dohme Research Laboratories
Jeremy Rifkin, Foundation on Economic Trends
Jane Rissler, Environmental Protection Agency
Anthony Robbins, Committee on Energy & Commerce, U.S. House of Representatives
Edward Lee Rogers, Attorney
Eugene I. Rosanoff, Wyeth Laboratories
Cris Russell, Washington Post
Lesley M. Russell, Subcommittee on Oversight & Investigations,
U.S. House of Representatives
Harold Schmeck, New York Times
Mark Segal, Environmental Protection Agency
Janet Shoemaker, American Society for Microbiology
Smita K. Siddhanti, University of Pittsburgh
Paul E. Stern, University of Florida
Clarence E. Styron, Monsanto Company
Donna B. Suchmann, Hazleton Biotechnologies Corporation
Marjorie Sun, Science Magazine
Laura Tangley, Bioscience
Jeff Trewhitt, McGraw-Hill World News
Vitolis E. Vengris, Food and Drug Adminstration
Robert J. Wall, Department of Agriculture
Judith A. Woods, Law Offices Daniel Thompson
Judith Wortman, American Institute of Biological Sciences
Stephanie Zobrist, Embassy of Switzerland

I. CALL TO ORDER AND OPENING REMARKS

Mr. Mitchell, Chair, called the meeting of the Recombinant DNA Advisory Committee (RAC) to order. He noted that 22 members of the 25 member committee were present and constituted a quorum. Mr. Mitchell said the matters the committee would consider were published in the Federal Register of September 20, 1984, in compliance with requirements for thirty days of public notice.

Mr. Mitchell announced he would recognize individuals in the following order: primary reviewers; other RAC members; ad hoc consultants; non-voting representatives to RAC; RAC's administrative staff; members of the public who submitted written comments; and finally other members of the public who wish to comment.

II. MINUTES OF THE JUNE 1, 1984, MEETING

Mr. Mitchell called on Mr. Daloz to review the minutes (tab 1191) of the June 1, 1984, RAC meeting. Mr. Daloz said he and Dr. Harvin had reviewed the minutes of the June 1, 1984, meeting and found them to be in order. He moved that RAC accept the minutes as written. Dr. Harvin seconded the motion.

Dr. McGarrity asked whether the attachments mentioned in the text of the minutes would be attached by NIH staff to the final version of the minutes. Dr. Gartland said NIH staff would add the attachments to the minutes before publication.

Dr. Walters questioned the use of the word "exotoxinosis" in item VI, Proposal to Clone Shiga-Like Toxin Gene from E. coli. Mr. Mitchell asked NIH staff to check this word for veracity and accuracy.

By a unanimous vote the RAC accepted the minutes of the June 1, 1984, meeting.

III. REPORT OF THE WORKING GROUP ON RELEASE INTO THE ENVIRONMENT

Mr. Mitchell called on Dr. McGarrity, Chair of the RAC Working Group on Release into the Environment, to report (tabs 1189, 1190) on the activities of that working group.

Dr. McGarrity said the Working Group on Release into the Environment is composed of twelve individuals: eleven biologists with expertise in plant biology, molecular biology, and ecology, and one lawyer. The working group also has representatives from the U.S. Department of Agriculture (USDA), the Food and Drug Administration (FDA), and the Environmental Protection Agency (EPA), and ad hoc consultants.

Dr. McGarrity said the Working Group on Release into the Environment had presented to RAC at the June 1, 1984, meeting a "points to consider"

document offering guidance to investigators wishing to submit for NIH approval under Appendix L of the NIH Guidelines experiments involving "release to the environment" of plants containing recombinant DNA. The RAC had unanimously accepted that document.

Dr. McGarrity said the working group subsequently began to prepare a "points to consider" document offering guidance to investigators wishing to submit for NIH approval proposed experiments involving "release to the environment" of microorganisms modified using recombinant DNA techniques.

Dr. McGarrity said the working group in preliminary structuring of the document focused on three issues: (1) Is the organism unique? (2) What is the probability of establishment in the environment of the recombinant organism or the recombinant DNA it contains? (3) What is the probability of the organism or a product of the organism causing harm?

Dr. McGarrity said the preliminary draft document requests: a summary of the proposed research including objectives, significance, and justification; characteristics of the modified organism and the parental organism; the source and nature of the introduced DNA sequences; the procedure by which the genes were inserted into the host organism; information on the stability and expression of the modified organism; a comparison of the modified organism to the parental organism; and an evaluation of the biological interactions that may result as a consequence of the release. The document also requests a description of the trial site, and microbiological and environmental monitoring.

Dr. McGarrity said proposals will be reviewed on a case-by-case basis; rigid guidelines or rigid criteria to assay or monitor any particular submission proposal will not be established. The finished "points to consider" document will be a guidance document which will not be incorporated into the NIH Guidelines.

Dr. McGarrity said the working group had some misgivings about sending the draft document to RAC at this time. This draft is not a final document but a preliminary working document which will inevitably be revised. Some working group members have not yet seen the entire draft document. The working group recognizes, however, the importance of these issue and wishes to offer RAC a progress report now; it hopes to present a final version of the "points to consider" document at the next RAC meeting.

Mr. Mitchell asked Dr. Sharples whether she thought the most important environmental questions had been included in the draft document. Dr. Sharples replied the major considerations had been incorporated in the draft document.

Dr. Gottesman said "uniqueness" is one important issue which the working group should address; i.e., if a modified organism is similar to an organism already existing in nature, then perhaps a proposed field trial of such an organism need not be as extensively evaluated as a field trial of a novel organism.

Dr. McKinney suggested the document's preamble should indicate Institutional Biosafety Committees (IBCs) review and approve of submissions prior to RAC review. Dr. Gottesman did not agree that prior IBC review should always be required. Dr. McGarrity also questioned whether IBC review should be required prior to RAC review. He said RAC and its working group might possess broader expertise than a local committee, and the IBC might wish to wait until they had the benefit of RAC review before approving a proposal.

Mr. Mitchell recognized Mr. Lee Rogers the legal counsel of the Foundation on Economic Trends.

Mr. Rogers said the document prepared by the Working Group on Release into the Environment does not constitute an environmental assessment on deliberate release experiments and does not bring NIH into compliance with the National Environmental Policy Act on deliberate release experiments. He said "an environmental assessment would have to discuss alternatives to the deliberate release experiments to be an environmental assessment on deliberate release experiments." He said the working group document contains no discussion of "alternative modes of analysis or alternative contained experiments that would provide all or some part of the data that would be attained with actual field experiments."

Mr. Rogers added that the working group document:

> "...fails to...call for procedures for assessing the data that's to be collected. That is, this document does not call for any scientific protocols that would enable the NIH to ascertain, minimize, the risk of deliberate release experiments."

Mr. Rogers said the working group document did not include standards of expertise, personnel, or quality of required data; and reviews are "conducted without any such standards of either quality or quantity in these areas and instead are informal, entirely on a case-by-case basis, without structure and assurance of requisite interdisciplinary expertise."

Mr. Rogers also contended the working group document:

> "...does not provide sufficient evidence and analysis for determining whether or not to prepare an environmental impact statement or a finding of no significant impact, either as to deliberate release experiments generally or for individual experiments."

Mr. Rogers said the language in the working group document which states "results from preliminary field tests will be the best test for unexpected consequences" acknowledges a failure to develop a predictive ecology to date. Mr. Rogers believed a science of predictive ecology could be developed. He also believed field testing could be simulated in contained systems, and asked the committee to "wrestle with" this issue.

Mr. Mitchell asked Mr. Rogers to clarify his definition of the word "alternative." Mr. Rogers said the word "alternative," meant "alternatives to

deliberate release experiments." If the goals of the experiments can be attained in other ways, these methods should be adopted. If the investigator can demonstrate that all possibilities for obtaining the information or attaining the goal in any other way than field testing were exhausted, this might be adequate demonstration that alternatives had been considered.

Dr. McGarrity said Mr. Rogers misinterpreted the purpose of the working group document. The working group document is intended to aid investigators in preparing proposals for review under the NIH Guidelines; it is not intended to provide directions on preparing environmental assessments (EAs). Dr. McGarrity reemphasized that the document before RAC was a preliminary draft which would undoubtedly be revised.

Dr. Gottesman said it is naive to imagine that a series of contained tests could generate all the necessary information. Small-scale field testing should be permitted in situations where data indicate field testing is reasonable. The results of the small-scale field test will indicate whether large-scale field testing should be permitted. The appropriate approach is to perform the field test, monitor it carefully, and evaluate the results.

Dr. Clowes said Mr. Rogers' wish to establish standard scientific protocols is simplistic; standard protocols cannot be devised at this time because of the diversity of potential organisms and environments. The Working Group on Release Into the Environment believes the most realistic, safest procedure is to evaluate proposed field tests on a case-by-case basis. Dr. Clowes said the experiments would be evaluated in decreasing levels of containment: first in the laboratory; then in contained systems such as growth chambers and greenhouses. The experiments will be performed in limited field tests only after testing in laboratories and greenhouses.

Mr. Jeremy Rifkin of the Foundation of Economic Trends said genetically engineered organisms are alive, unpredictable, can reproduce, migrate, and cannot be recalled. He contended that if a predictive ecology cannot be developed because the variables are too great, society:

> "...ought to reevaluate whether we want to start a process when we start authorizing and introducing for field experiments not three experiments, but hundreds and then thousands of experiments, over the coming decade."

Dr. Pimentel asked clarification of the statement in the preamble of the working group document that "if the probability of any one of these factors is zero, the risk should be considered zero."

Dr. Gottesman offered the example of an organism capable of causing a great deal of ecological harm if it survived in the environment but where the probability of its surviving in the environment was zero; in this case, the risk would be zero.

Mr. Mitchell extended his appreciation to the Working Group on Release into the Environment for the tremendous amount of time and effort expended on this difficult topic.

Mr. Mitchell asked Dr. McGarrity to report on planning for the national symposium on release of genetically modified organisms into the environment which Representative Albert Gore had asked the American Society for Microbiology (ASM) to organize. Dr. McGarrity said the ASM is currently contacting other scientific societies to elicit help in planning the program. The ASM hopes to hold this meeting in the spring of 1985.

IV. REPORT OF THE RISK ASSESSMENT SUBCOMMITTEE

Dr. Gottesman said Assistant Secretary for Health Brandt has requested the RAC Risk Assessment Subcommittee to evaluate a series of questions involving recombinant DNA risk assessment (tab 1188). These questions originated in the Office of the Assistant Secretary for Planning and Evaluation (ASPE) of the Department of Health and Human Services (DHHS). Dr. Gottesman said she as Chair of the RAC Risk Assessment Subcommittee had polled subcommittee members on the issues and had collated the responses in order to develop a draft response. The subcommittee met by telephone conference call on October 15, 1984, to evaluate this preliminary draft response.

Dr. Gottesman said the first question in the ASPE memorandum asked whether the existence of transposable elements complicates the estimates of risk in the cloning of deleterious genes. She said the subcommittee agreed the existence of such elements was implicitly taken into account in experiments performed to estimate plasmid mobilization frequencies.

Dr. Gottesman said the second question posed by the ASPE memorandum concerned the sensitivity of assays for plasmid transfer. She said the subcommittee felt many existing assays are extremely sensitive.

Dr. Gottesman said the third question asked how the potential impact of altered host range in deliberately released genetically engineered organisms could be assessed. Dr. Gottesman said the subcommittee recognizes host range is an important issue in evaluating whether to allow field tests of organisms containing recombinant DNA. The subcommittee did not, however, see any general approach which would help resolve that issue prior to evaluation of each proposal on a case-by-case basis.

Dr. Gottesman said the fourth question asked whether the use of broad host range plasmids complicates risk assessment studies. The subcommittee agreed that if field testing of organisms containing broad host range plasmids is proposed, questions would be posed that may not have been asked in earlier risk assessment studies.

Dr. Gottesman said the fifth question of the ASPE memorandum asked whether human "oncogenic retroviral plasmids" could be transferred to indigenous gut flora and pose risk for laboratory workers. Dr. Gottesman said the

subcommittee did not feel it possessed sufficient virology expertise to adequately address this question and suggested the opinion of virologists be sought.

Dr. Gottesman said the sixth question asked whether gene expression levels calculated several years ago are still relevant. Dr. Gottesman said these estimates were based on the assumption that the maximum level of protein synthesis that could theoretically be turned over to production of a foreign protein had been turned over to synthesis of the product of the introduced gene. These original estimates are still valid.

Dr. Gottesman said the seventh question in the ASPE memorandum asked how use of high copy number plasmids might affect estimates of toxin production and gene transfer probability. The Risk Assessment Subcommittee agreed the issues involved in use of high copy number plasmids have already been factored into the calculations of maximum theoretical levels of protein synthesis.

Dr. Gottesman said the eighth question dealt with the survival and effects of various bacteria in the environment. This question is very complex; since each proposed application will be reviewed on a case-by-case basis, the issues will be addressed at the time each proposal is reviewed.

Dr. Gottesman said the ninth question in the ASPE memorandum dealt with shuttle vectors and retrovirus vectors. The subcommittee pointed out that the most important consideration in evaluating the potential for spread of a defective vector will be the availability of helper virus.

Dr. Gottesman said the tenth question asks whether cosmid vectors pose any special risk. The subcommittee pointed out that is most cases cosmids are more contained than the bacterial virus from which they are derived.

Dr. Gottesman said the eleventh question asks whether nonconjugative plasmids could be disseminated via transfer events involving transient survival of conjugative plasmids. The Risk Assessment Subcommittee said the type of plasmid to be used in a protocol is an important consideration in the review process.

Dr. Gottesman said the twelfth question in the ASPE memorandum asks whether virulence or others factors may exist which could affect the spread of plasmids. She said this question was open-ended and difficult to address.

Dr. Clowes said much new information concerning plasmids, bacteriophages, cosmids, etc., has been accumulated in the years since the NIH Guidelines were first established. The Risk Assessment Subcommittee in reviewing this additional information determined that earlier containment conclusions were still appropriate since the initial evaluations were often done on a "worst case" basis. In addition, the subcommittee did not identify any important generalizable risk assessment experiments which should be done.

Dr. Holmes said the Risk Assessment Subcommittee agreed designing risk assessment experiments to address general issues raised in the ASPE memorandum would be very difficult. The experiments currently being submitted to RAC for evaluation should continue to be reviewed on a case-by-case basis.

Dr. McGarrity suggested the Risk Assessment Subcommittee respond directly to the ASPE memorandum without first submitting their response to RAC for review. The subcommittee could simply report to RAC at the next meeting. Dr. McKinney agreed. He said the Assistant Secretary for Health did not stipulate the full RAC should consider these issues but rather asked that they be reviewed by the RAC Risk Assessment Subcommittee.

Dr. Sharples said the information generated by the Risk Assessment Subcommittee should, however, be available to RAC.

V. ADDITIONAL ANNOUNCEMENTS

Mr. Mitchell said RAC's charter was renewed by the Secretary, HHS, in June 1984. A revision was introduced into the charter at that renewal: RAC members may serve after the expiration of their terms until their successors have been appointed. Mr. Mitchell said the terms of six RAC members, Drs. Holmes, Fedoroff, McGarrity, McKinney, Levine, and Scandalios, expired in June 1984. These members have kindly consented to continue to serve until successors have been appointed.

VI. PROPOSED AMENDMENT OF SECTION III-D OF THE NIH GUIDELINES

Mr. Mitchell asked Dr. McKinney to present this proposal to amend the NIH Guidelines (tabs 1181, 1186/I). Dr. McKinney said Mr. C. Searle Wadley and Dr. John H. Keene of Abbott Laboratories, North Chicago, Illinois, in a letter dated August 21, 1984, proposed the following sentence be added to Section III-D of the NIH Guidelines:

> "Although these experiments are exempt, it is recommended that they be performed at the appropriate biosafety level for the host or recombinant organism (for biosafety levels see 'Biosafety in Microbiological and Biomedical Laboratories')."

Dr. Landy felt this language stated the obvious but was not opposed to including it in the NIH Guidelines. Drs. Holmes and Levine also concurred.

Dr. McKinney said he felt the language would more appropriately be included as a new last paragraph of the narrative section of Appendix A. Dr. McGarrity agreed with Dr. McKinney's analysis. He felt the authors' intent could be met by including the proposed language in Appendix A.

Dr. McKinney moved the proposed language be included as a new third paragraph of the narrative portion of Appendix A of the NIH Guidelines. He also

suggested the full reference to the booklet "Biosafety in Microbiological and Biomedical Laboratories" be included. Dr. McGarrity seconded the motion.

The RAC recommended the motion be accepted by a vote of twenty-two in favor, none opposed, and no abstentions.

VII. REPORT OF THE WORKING GROUP ON HUMAN GENE THERAPY

Mr. Mitchell called on Dr. Walters, the Chair of the RAC Working Group on Human Gene Therapy, to offer a progress report on the activities of that group.

Dr. Walters said his report will describe: (1) the mandate and history of the working group; (2) the membership of the group; (3) the "points to consider" document being developed by the working group; and (4) a timetable for completing the document.

Dr. Walters said RAC at the September 19, 1983, meeting accepted responsibility in principle for reviewing human gene therapy protocols. At the February 6, 1984, meeting, RAC operationalized this acceptance. Language was added to Section III-A of the NIH Guidelines requiring protocols involving human gene therapy be reviewed by RAC and approved by the IBC and the NIH before initiation. A Working Group on Human Gene Therapy comprised of members from the basic sciences, clinical medicine, ethics, and law was formed during the summer 1984 and held its first meeting on October 12, 1984.

Dr. Walters said the Working Group on Human Gene Therapy is composed of fifteen members plus executive secretary (Attachment II). He categorized the members as follows: four laboratory scientists, three clinicians, three ethicists, three lawyers, and two public policy experts. The working group also has a consultant on retroviruses and representatives from the NIH Office of Protection from Research Risks (OPRR) and the FDA.

Dr. Walters offered the RAC a draft outline (Attachment III) of the document being developed by the working group; that document is to be entitled "Points to Consider in the Design and Submission of Human Gene Therapy Protocols." He emphasized that the draft outline represents the current trend of the group's thinking and will undoubtedly be modified.

Dr. Walters said the document's preamble will: (1) Indicate the document focuses on somatic cell gene therapy. The working group does not foresee germline gene therapy being applied to humans in the near future. (2) Note that the working group has based some of the draft document on DHHS regulations involving human subjects and on the report "Splicing Life" by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. (3) Outline the review procedure for human gene therapy protocols. The IBC and the Institutional Review Board

(IRB) would first review the protocols. The proposals would then be forwarded to the Working Group on Human Gene Therapy for review. The RAC will subsequently review the proposals. The NIH Director has final authority to approve or reject proposals. (4) Describe a procedure for periodic revision of the points to consider document. Gene therapy is a very dynamic field, and the working group anticipates enough new information will be generated yearly to require revision of the document.

Dr. Walters said the first section of Part I of the points to consider document will refer to the DHHS Regulations for Research Involving Human Subjects (45 CFR Part 46). These regulations apply to human gene therapy protocols. In addition, this part of the document will require specific types of information be provided by the investigator(s) on: (1) research design, risks and benefits; (2) the selection of subjects; (3) the informed consent process; and (4) protection of privacy and confidentiality.

Dr. Walters said the section of the document entitled "Research Design, Anticipated Risks and Benefits" will first ask the investigator to describe objectives and rationale for the proposed gene therapy. What is the disease to be treated? Why was this disease chosen for therapy? Why was this approach to therapy chosen? What is the natural history of the disease? What alternative treatments are available and have these therapies been considered?

Dr. Walters said the document will then ask for a description of research methods including detailed information on the structure of the genetic information to be introduced into the patient. The document may request information on animal and tissue culture studies including perhaps laboratory cell culture studies performed with the patient's cells.

Dr. Walters said questions on clinical and public health considerations in the treatment of patients will be posed. How will therapy be administered to the patients? What kind of patient monitoring will be provided? At what intervals will the investigators report to the IRB and the Working Group on Human Gene Therapy?

The document will also request information on the investigators' qualifications and the adequacy of the facilities.

Dr. Walters said the section dealing with subject selection is concerned primarily with issues of equity and fairness. Human gene therapy will be a scarce biomedical resource, at least in the early days; and the working group would like to ensure that patients have equal access.

Dr. Walters said informed consent for human gene therapy may be complicated because of the the complexity of the technique, but also because the first subjects are likely to be pediatric patients whose parents will be making judgments on their behalf.

Dr. Walters said the section dealing with protection of privacy and confidentiality will ask the investigator whether measures could be taken to

prevent the kind of circus-like atmosphere that sometimes surrounds medical firsts.

Dr. Walters said the working group feels part of its mandate is to inquire about broader issues, and Part II of the points to consider document will raise broader social questions. For example, it might ask what effect, if any, the proposed somatic cell gene therapy is likely to have on the reproductive cells of treated patients. It might also inquire about possible commercial aspects of the particular gene therapy protocol including the possibility of patenting the technique. These types of questions were raised in reports such as "Splicing Life."

Dr. Walters said Part III of the document will request documentation including a copy of the original protocol or grant application in which the gene therapy technique is described.

Dr. Walters said the first draft of the document was discussed at the October 12, 1984, plenary meeting of the Working Group on Human Gene Therapy. This meeting was announced in the Federal Register and open to the public. Subgroups of the working group were then formed to revise portions of the document. The resulting draft is to be discussed at a working group meeting on November 16, 1984. This meeting has been announced in the Federal Register and will be open to the public. The document which emerges from that meeting will be circulated to all RAC members for comment. When those comments have been incorporated, public comment will be solicited by publishing the draft document in the Federal Register and sending it to individuals and religious groups interested in the issues posed by human gene therapy. The document will be revised in light of public comment and the working group will subsequently submit the document for RAC review at the next RAC meeting.

Dr. Gottesman emphasized that in the review of individual proposals, the working group expects many IRB concerns will "overlap" with concerns discussed in the "Points to Consider." However, IRB concerns will focus specifically on risk/benefit considerations for the particular patients; and the working group anticipates there will be both scientific and social issues that a broader group such as RAC or its working group can approach more easily than local committees. Dr. Gottesman emphasized that the working group document focuses on somatic cell gene therapy as the first proposals presented to RAC undoubtedly will involve somatic cell therapy experiments.

Dr. McGarrity asked whether IRBs and IBCs would be required to review and approve of proposals prior to NIH review. If local committees must review proposal prior to NIH review, would local committees be responsible for evaluating the entire proposal? Would RAC and its working group offer advice and support to local committees should these committees be uncomfortable evaluating proposals prior to RAC review?

Dr. Walters said the working group feels local committees should review and approve proposals prior to NIH review. He hoped the points to consider document would provide guidance to IRBs and IBCs.

Dr. Gottesman said the working group realizes a heavy burden will be placed on local committees by prior review requirements, but the working group feels IRB evaluation of protocols with respect to protecting the individual patient's interests is important. The IRB could request NIH consideration of specific aspects of protocols.

Dr. McGarrity asked if an IRB might abstain from voting on a protocol; would there be another mechanism to send the proposal to NIH review or would it simply die at the local level if they did not wish to vote on that particular proposal.

Dr. Gottesman felt that while the IRB would at some point have to approve the proposal, the working group and RAC could probably accept tentative IRB and IBC recommendations. RAC could review the proposal and subsequently return it to the local committees for final action.

Dr. Rapp felt local committees should have the opportunity to evaluate proposals prior to NIH review, although they should have the option of asking NIH for input.

Dr. Landy asked what would happen if RAC determined that one hospital or one clinician is qualified to perform an experiment but another institution submitting an identical proposal is not.

Dr. Rapp asked whether review will be on a "case-by-case" basis or an "institution-by-institution" basis.

Dr. Walters replied the working group believes review should be on a case-by-case basis. Empirical data and normative judgements form the basis of review, but the working group will attempt to make the process as objective and neutral as possible. Dr. Walters said the Working Group on Human Gene Therapy does not intend to function as a peer review body. The working group will simply determine whether the investigator and the facilities meet a minimum threshold of competence.

Dr. McKinney asked whether mechanisms were in place to deal with privacy and confidentiality issues.

Dr. Walters said Dr. McKinney's question raises two concerns: (1) the privacy of the patient; and (2) the protection of proprietary information. Dr. Walters said the working group and RAC will attempt to protect the privacy of the patients. Protocols could be reviewed without reference to the names of patients. Dr. Walters said the working group has not yet addressed proprietary issues other than that the points to consider document will ask the investigator's intentions regarding patents or trade secrets. The working group anticipates that patent questions and trade secrecy will not be a major issue in human gene therapy.

Dr. McGarrity asked whether diseases exist in which the intervention must occur within the first few weeks of a patient's life. Would such diseases present a problem if the total review process requires three or four months?

Dr. Anderson said some diseases should be treated at birth or even prenatally. He said the length of time required for review might be a potential problem for such patients in future applications. In the initial cases, however, human subjects will be selected only after the protocols are reviewed and approved. One of the first cases will probably be severe combined immune deficiency disease (SCID) caused by ADA deficiency. There are only about 50 reported families in the world with this disorder. While these patients are rare, they are ideally suited to be the first subjects of gene therapy, because they can be cured by bone marrow transplantation.

Mr. Rifkin said he was concerned because the working group had chosen to discuss only somatic cell gene therapy at this time, and to ignore the issues associated with germline human gene therapy. He said previous studies had dealt with both somatic and germline applications in the same context.

Mr. Rifkin felt it was inappropriate to treat these two categories separately because "there might be some correlation between certain somatic gene experiments and some effects on the germline or the reproductive cells." He asked whether long-term effects of somatic cell experiments on the patient's germline could be detected. Mr. Rifkin said if any possibility exists that these experiments might affect the patient's germline, then it would be "inappropriate to move ahead knowing that speculation is possible and trying to isolate these two categories."

Dr. Walters said the task of RAC and the working group is to respond to individual proposals on a case-by-case basis and not to engage in a general discussion of global issues. The President's Commission has already discussed global issues. Dr. Walters said the working group will ask investigators to supply data from laboratory experiments to exclude the very slight possibility somatic cell gene therapy might have an effect on sperm or egg cells.

Dr. Rapp said the possibility a gene inserted into some other portion of the subject's body would transfer to the germ cells is extremely low.

Dr. Joklik said numerous experiments have been performed on various animal species from mice to chickens to insects. In no case had the introduced DNA been found to transfer to germ cells. Dr. Joklik said that at this time the probability of such an occurence is so low it is not a concern.

Dr. Landy said many current therapies have profound effects on the germline. He did not feel this consideration was unique to human gene therapy. Dr. Henry Miller of the FDA agreed various therapies have side effects. He said it is unreasonable to fixate on the effects to gametes to the exclusion of effects on cardiac or liver tissues.

Mr. Rifkin noted there are only three ethicists on the working group. He felt this number of ethicists did not represent a "good cross section of ethical and theological opinion on something as grave and potentially important to our society as human genetic engineering." He suggested the working group broaden its representation. He asked whether any religious leaders had been contacted or whether there had been an attempt to enlarge the working group to include the opinion of major religious leaders.

Mr. Mitchell said the working group is composed of fifteen members; three of these members are ethicists, two members are public policy experts who are also well versed in ethical issues. In addition, Drs. Walters and Childress have backgrounds in theology. Dr. Walters said the composition of the working group is similar to the composition of groups such as the National Commission for the Protection of Human Subjects, the Ethics Advisory Board, or the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. He said the "Points to Consider" document would be brought to the attention of a wide spectrum of people including major religious leaders.

Mr. Mitchell said because of the diversity of religious views in this country it is appropriate to solicit the opinion of individuals associated with various religious traditions, and this will be done.

VIII. PROPOSED ADDITION OF PROHIBITED EXPERIMENTS TO THE NIH GUIDELINES

Mr. Mitchell asked Mr. Rifkin to present his proposal (tabs 1182, 1183, 1184, 1186/II, 1187, 1194, 1195).

Mr. Rifkin said while closely related species may be bred by traditional practices, nature rather narrowly proscribes what can be accomplished. "Species walls, mating boundaries establish some limits as to the kind of recombinations that may occur through natural methods." Mr. Rifkin contended the experiments of Dr. Ralph Brinster of the University of Pennsylvania in which genes from one mammalian species are introduced into another species are qualitatively different from preexisting breeding programs.

Mr. Rifkin said to date the biological unit of manipulation has been the organism; now the unit of manipulation has become the gene. The unit of importance ceases to be the species itself, but rather the composition of genetic materials. Mr. Rifkin contended society is beginning a very long, protracted journey which will reshape our concept of life so that we will increasingly see the importance of life at the genetic level and not at the species level.

Mr. Rifkin said some researchers argue the human growth hormone gene transferred into mice by Dr. Brinster is not unique, that it's only a chemical. Mr. Rifkin said this argument is a form of scientific reductionism; if this gene is simply a chemical, then certainly every other gene that makes up the human species is simply a chemical. If there is nothing unique about transferring this gene and if the transfer of this gene poses no ethical,

moral, or public policy questions, "at what level would there be questions posed?" Would the animal have to take on human characterictics before a problem would be identified?

Mr. Rifkin asked RAC to develop detailed criteria. "What genes are permissible in the human gene pool to transfer to other species? What genes in the human gene pool are impermissible to transfer to other species?" If the committee decides such criteria cannot be developed, then all human genes could potentially be transferred to other species for some short-term medical or economic benefit. Mr. Rifkin said this possibility poses a major ethical and policy question.

Mr. Rifkin said every major scientist, institution, and association in the United States has responded to the Federal Register announcement of his proposals and almost all have stated that they find absolutely no ethical problems in transferring genes between species. Mr. Rifkin noted, however, that several commentators including Dr. David Baltimore, Director of the Whitehead Institute, wrote that some ethical questions might arise if genes from other species are transferred into the human germline. Mr. Rifkin said he could not understand why [illegible] into the human germline might pose an ethical problem while [illegible] human gene into the germline of other species would not pose a problem. He contended the NIH should have considered the ethical issues of transferring genes between species before funding Dr. Brinster's grant.

Mr. Rifkin in concluding his remarks said:

"Finally, [illegible] that even if that vote comes today the concerns of this committee might not be the concerns of the rest of the American public. [illegible] that many scientists think the American public are not [illegible] can't possibly understand all the complex questions raised [illegible] technology, that unfounded fears [illegible] I suggest that that is not a correct analysis. Genetic [illegible] gives us the most potentially powerful instrument [illegible] of this planet that we have ever had at our disposal [illegible] American public has every right to believe there are some ethical and social questions at each stage, and I would say that this stage is a fundamental precedent stage today. If this committee, by its vote, will say to the Director of the NIH that it is your opinion that there are no ethical problem as we proceed with this technology in transferring genetic traits between species, and therefore, it should be the accepted policy of the United States government to proceed."

Mr. Rifkin said Dr. Michael Fox, Scientific Director of the Humane Society of the United States and co-plantiff with the Foundation on Economic Trends in a lawsuit against the NIH, also wished to comment on the proposal.

Dr. Fox said he represents some quarter of a million members of the Humane Society and is "speaking for the animal kingdom." Dr. Fox said interferring with animal genomes raises ethical issues. Nature, in her wisdom, may well have set up species barriers for a particular purpose, i.e., for managing natural ecosystems and their coevolution.

Dr. Fox said just as there are multiple genetic detects in purebred dogs and cats as a consequence of selective breeding, use of recombinant DNA techniques may also jeopardize animal welfare. He said traditional breeding programs have produced animals with multiple inbred genetic defects, not for utilitarian purposes but for sheer esthetic reasons.

Dr. Fox said selective breeding of high yield strains of farm animals results in a variety of so-called "production diseases:" lameness, osteoporosis, growth abnormalities, metabolic disorders affecting magnesium and calcium levels, and many other health problems.

Dr. Fox said Dr. Brinster's idea is to create a pig or sheep that will grow twice as big, twice as fast. Dr. Fox asked what is saved if they will grow twice as big, twice as fast. He replied, "Time not food, because one never gets something for nothing." He contended Dr. Brinster's research has demonstrated that supplementation of dietary zinc is needed for the modified mice to grow normally. Dr. Fox said that before the need for zinc supplementation was discovered there was considerable animal suffering.

Dr. Fox said we are on the point of turning animals into biological machines. He said Dr. Brinster stated that genes for valuable proteins could be introduced into animals, and the protein products harvested from the blood or milk of these animals. Dr. Fox asked if modifying animals for this purpose is ethically and morally acceptable. He said the animal's soma will be modified if animals are made into biological machines; but "the psyche of the animal, its telos, its intrinsic nature" will not be affected. In such a situation, the mind of the animal may be trapped in a totally alien body. He asked RAC to address this issue.

Dr. Fox said an environmental impact assessment should be done if introduction of genetically modified microorganisms into the intestines of animals is proposed. He also said that perhaps a person with veterinary or animal science expertise should be appointed to RAC.

In regard to what mankind is going to do to the animal kingdom, Dr. Fox urged the committee to consider the word "dominion" which he said is not derived from the Latin word "domino," to rule over, but from the Hebrew word "rache," to steward with compassion and understanding.

Dr. Clowes said RAC has received an impressive body of letters almost all opposing Mr. Rifkin's proposal. He asked the assembly's indulgence as he quoted from several letters.

Dr. Clowes said one philosophical argument advanced by a number of geneticists and stated by Dr. Maxine Singer of the National Institutes of Health is that:

> "The notion that a species has a telos (a purpose) contravenes everything we know about biology. A species can have, and may in the past have had a telos (an end) namely extinction. That is the only telos known to exist. No species we know of has a fixed genome. Quite the contrary. Genetic studies throughout this century have again and again confirmed that the genetic makeup of organisms within a species is continually changing through recombination, mutation, deletion, duplication, rearrangement and the insertion of DNA sequences. Recent experiments have, in anything, shown us that this remarkable plasticity is more extensive than we imagined and is a fundamental property of living matter."

Dr. Clowes said a number of letters emphasized the potential practical aspects of gene transfer experimentation. Dr. Donald Brown, Director, Carnegie Institution of Washington, states:

> "The introduction of foreign genes into the germline of mammals other than humans has many potential benefits for mankind. Genetic changes by modern methods can be done rapidly and with much greater precision than conventional breeding and selection programs."

Dr. Clowes then quoted from a letter from Dr. David Kunkle, Assistant Professor at the University of Texas Medical Branch at Galveston who wrote he opposed Mr. Rifkin's proposal because:

> "If adopted...[the proposal] would have a most far-reaching adverse impact on a promising future approach to the treatment of human genetic diseases. Some of these diseases caused by enzyme deficiencies in a well-defined target area may soon prove amenable to treatment by somatic gene therapy in which the wild type gene would be introduced in somatic cells of the affected organs.... Obviously, detailed animal experiments would have to precede any possible human trials of such a scheme. Since animal models of only a few genetic diseases are available, most of such experiments would attempt to detect expression of exogenous genes against a wild type background. To establish definitively the nature of any increased expression, heterologous genes would have to be used. But it is precisely those experiments which Mr. Rifkin now seeks to ban. Thus, his proposal would forever seal off this promising area of research."

Dr. Clowes said the American public had expressed its point of view on this topic and called attention to the several hundred letters from individuals opposed to the proposed prohibition. Dr. Clowes quoted from a letter from Ms. Kristie Baird of Elizabethtown, Kentucky, who wrote, "I believe that anytime it is possible to save people's lives, it should be done."

Dr. Friedman first addressed Mr. Rifkin's statement that the American public is not educated. Dr. Friedman said in fact the American public is educated and has made a basic decision that research on animals to ameliorate human disease is not only acceptable but should be done.

Dr. Friedman said one person's ethics may differ from another's. In his mind, treating human diseases and alleviating human suffering is a primary moral imperative. Dr. Friedman said Mr. Rifkin's proposal would eliminate one method of researching certain diseases and making broad gains in the therapy of these diseases.

Dr. Friedman said the language of Mr. Rifkin's proposal is very vague. For example, the term "genetic trait" is used but not defined. One could argue that a whole gene could be transferred without affecting a genetic trait; e.g., eye color may depend on a number of genes, and transferring one of these genes may not change eye color.

Dr. Friedman said it is difficult to define a unique gene because in some cases the gene of one species differs from the gene of another species by a single base pair. The differences within members of the species may be more broad than the differences between the species. In addition, gene exchange between species probably occurs in nature; viruses pick up genetic material and probably carry such material across species lines.

Dr. Gottesman reviewed the current status of gene transfer experiments under the NIH Guidelines for Research Involving Recombinant DNA Molecules: (1) any experiment which involves the introduction of recombinant DNA into humans must be reviewed by RAC and approved by NIH; this would include both proposed introduction into somatic or germline cells although no germline experiments are anticipated in the near future; and (2) experiments in which recombinant DNA is introduced into animals are covered by Section III-B of the Guidelines and are subject to review and approval by the local IBC.

Dr. Gottesman said gene transfer experiments are an important tool through which questions about gene regulation and the development of complex systems such as animals or humans can be addressed. She pointed out that at this time no other method exists for approaching these types of studies. Dr. Gottesman said these studies will result in advances in treating human diseases, in treating animal diseases, and in using animals more efficiently as food sources. She said Mr. Rifkin's proposal would prohibit these types of experiments and would stop extremely important research.

Dr. Gottesman said she is aware of the controversy surrounding the ethics of using animals in research; however, the viewpoint that animals should not be used in research is one which she did not share. She did not think the majority of people in this country shared this viewpoint. She thought most people would come down very strongly in favor of using animal models to test disease therapies.

Dr. Gottesman said she was overwhelmed by the number of letters received in response to the Federal Register announcement of the proposed prohibition. Anyone who has attempted to obtain public response to any type of announcement knows how hard it is to obtain comments. Yet in addition to the approximately fifty letters from scientists who considered it important to write both for their own research and for society's ability to treat human disease or deal with hunger, over 250 letters have been received from the general public. Dr. Gottesman said clearly a number of people in this country consider this type of research extremely important.

Dr. Gottesman recommended that RAC not only not pass the proposed amendment to the Guidelines, but she urged RAC to approve a motion indicating that RAC considers gene transfer experiments to be very important research which should be fostered.

Dr. Landy said the American people are entitled to an intelligent and rational discussion of the ethical issues raised by technological advances. Dr. Landy felt, however, Mr. Rifkin had behaved irresponsibly in ignoring all that is known about genetics and evolution and had obfuscated the issues.

Dr. Landy said increasing the human lifespan has increased the world population. Technology for producing more food, more efficiently is necessary. Dr. Landy quoted from a letter from Dr. Charles Yanofsky of Stanford University:

> "Modern medicine has already done much to keep individuals with genetic defects alive to the child-bearing age and beyond. Since society and the medical profession welcome these efforts, we must not prohibit exploration of any possibility of correcting a serious genetic defect."

Dr. Landy said many of the undesired consequences of animal breeding alluded to by Dr. Fox are a result of limitations in animal husbandry. Recombinant DNA technology may allow introduction of a particular desirable gene into an animal without introducing undesirable traits, and this is an argument in favor of continuing research in this area.

Dr. Landy said he was impressed by the number and breadth of the letters the NIH received concerning Mr. Rifkin's proposal. There are letters from high officers of academic and research institutions, not only in the sciences but also in the humanities and law; letters from individual scientists engaged in research and education, including many of recognized international stature; letters from private foundations dedicated to improvement of human welfare; letters from organizations and individuals concerned with animal husbandry and efficiency of food production; letters from medical practitioners and educators in health care delivery; and rather touching letters from individual citizens concerned about the future prospects for solutions to now intractable health problems.

Dr. Wensink said the issues are clear cut and well-described. He thought clearly defined potential benefits have been enumerated and are opposed by unsupported, mythical fears of risks.

Dr. Bowman said gene transfer may be the only feasible way of curing a disease such as cystic fibrosis. She said to even consider stopping the gene transfer research needed to address this disease is out of the question.

Dr. McKinney said he wished to point out that in addition to proposing modifications to the NIH Guidelines, Mr. Rifkin has chosen to interpret how the NIH should apply the proposed modifications; Mr. Rifkin contends the NIH should extend its purview to commercial companies engaged in recombinant DNA research under a licensing agreement with an NIH funded institution which cited the NIH Guidelines in the licensing agreement. Dr. McKinney said Mr. Rifkin was attempting to involve the NIH, which is not a regulatory agency, in an area where it has no authority. Dr. McKinney urged the RAC to reject Mr. Rifkin's proposal.

Dr. McGarrity said Mr. Rifkin's statement that RAC ignores the public is false. Public members have long been part of RAC's composition, and RAC has actively sought to include the public in its deliberations. Dr. McGarrity said Mr. Rifkin underestimates the intelligence and knowledge of the public. Dr. McGarrity stated that Mr. Rifkin's contention RAC would be saying there are no ethical problems if Mr. Rifkin's proposals are not approved is utter nonsense. Dr. McGarrity said major points of concern exist, but the scientific approach examines the data and bases a decision on a case-by-case review.

Dr. Walters responded to Mr. Rifkin's implication that RAC has always given permission to proceed. Dr. Walters noted that until recently NIH procedures permitted the local IBCs and IRBs to approve human gene therapy protocols without RAC review and NIH approval. The NIH Guidelines were revised to require the much more rigorous process of national review.

Dr. Walters said transfer of genes into the human germline would involve the use of in vitro fertilization (IVF). NIH funded IVF research is currently under a de facto moratorium; national review by an Ethics Advisory Board is required, and at present, such a board does not exist.

Dr. Walters said animal welfare, either in the laboratory or in animal husbandry, is a real issue. RAC, however, is not the appropriate group to address this issue. Some states have animal welfare rules and the NIH Office for Protection from Research Risks is participating in the process of revising existing Public Health Service animal welfare guidelines. Dr. Walters felt local review committees charged with animal welfare are the appropriate bodies to deal with this issue. Dr. Walters suggested RAC reject Mr. Rifkin's proposal in light of the potential benefits gene transfer research might provide.

Dr. Fox thought public support of gene transfer research is based on fear of death and suffering. He said Aristotle's original meaning of "telos"

was not a final endpoint but the organism's intrinsic nature expressed in the here and now. Society's responsibility is to the present not to the future. He said we are not progressing anywhere.

Dr. Fox contended that what is often regarded as progress is simply dealing with residual problems passed from one generation to the next. He said humans have a tremendous responsibility to the animal kingdom, and he is concerned with RAC's human-centered rhetoric and rationalizations. He said he had to leave to wash his hands.

Dr. Miller said he wished "to address some glaring factual errors in Dr. Fox's remarks in what I thought was otherwise a rather absurd presentation." Dr. Miller said early field trials of bovine growth hormone in dairy cows suggest the cows utilize food stocks more efficiently with as much as a 15 percent improvement in milk output without a concomitant increase in food consumption, in effect, "getting something for nothing" through improved nitrogen utilization.

Dr. Miller said Dr. Fox had not understood the function of zinc supplementation in the diet of Dr. Brinster's genetically engineered mice. Dr. Miller explained that the recombinant vector was constructed so that the human growth hormone gene is under the control of a zinc-sensitive promotor. Dietary zinc supplementation increases the activity of the human growth hormone gene, and the mice grow larger than normal. However, in the absence of zinc supplementation, they are of normal size and do not suffer.

Dr. Miller said adopting Mr. Rifkin's proposal would inflict incalculable harm on several very important areas of scientific inquiry; e.g., the study of genetic susceptibility to diseases such as breast cancer. Harm would also be inflicted on research aimed at developing therapies for human genetic diseases since animal studies which are necessary prior to human clinical trials could not be carried out.

Dr. Miller said Mr. Rifkin's proposal is:

> "...yet another highly contrived issue that is another manifestation of what 'Nature'...alluded to in characterizing Mr. Rifkin as someone whose nuisance to substance ratio is high."

Dr. Joklik said he questioned what he was hearing when the proposition is made that progress is not only elusory but possibly even undesirable, or when the implication is made that the health of this nation is no better today than it was 100 years ago, or when the discussion centers on what was in Aristotle's mind when he used certain phrases.

Dr. Joklik said the practical benefits of this type of research for humankind is unquestionable; the evidence supporting this position is irrefutable. He called absurd the proposition that the prospect of benefit to untold humans through generations to come should be outweighed by putative discomfort to a small number of laboratory animals.

Dr. Joklik said a concept of "species" was being invoked in support of Mr. Rifkin's proposals. Dr. Joklik said he is a member of the International Committee for the Taxonomy of Viruses which has been trying to develop a definition of species with regard to viruses. Dr. Joklik said it has been utterly impossible for this committee to arrive at a definition of a species. Species are constantly evolving, and the transfer of genes from one "species" to another has occurred throughout evolution.

Dr. Joklik supported Dr. Gottesman's recommendation that RAC forcefully state research on gene transfer be fostered and not hindered.

Dr. Rapp supported Dr. Joklik's comments. He pointed out that medical research has tremendously benefited a variety of animal species. The development of a rabies vaccine is one example.

Dr. Rapp said Dr. Fox does not like the fact that humans are human-centered, but species tend to be self-centered. Dr. Rapp stated that stewarding and handling animals in a humane manner is important, but to think about preventing certain lines of research in any species is a very dangerous idea. If this concept were to be seriously supported, society should consider the "telos" of bacteria and viruses.

Dr. Rapp said he supported Dr. Gottesman's proposal that RAC issue a statement in support of this type of research. He agreed ethical issues might exist, but the consequences of forfeiting all benefits of gene transfer research for what at the moment appear to be extremely minor risks are so great that RAC should not support Mr. Rifkin's proposals.

Dr. Saginor said that:

> "...although some of Mr. Rifkin's original purposes may have been sincerely based, it appears that various catch phrases are uttered and written to engender public fear and potential press coverage with almost McCarthy-type tactics. I want to address a statement such as 'a quick vote'...by our committee. I resent the overt implications, and I resent this playing to potential inflammatory press quotes, and I particularly resent you implying that our committee and subcommittees do not care...and do not carefully consider various ramifications of our decisions before a vote is taken."

Dr. Saginor said it is important to address the issues and not strike fear into the American public. He said he strongly supports Dr. Gottesman's suggestion.

Dr. Gottesman moved that:

> "The RAC reject the amendments proposed by Mr. Rifkin and published in the Federal Register of September 20, 1984, Section II. Both its importance in current scientific research and the long-term possibilities for treatment of human disease and the development of more efficient

food sources make it a moral imperative that we strongly oppose the blanket prohibition of this class of experiments."

Dr. McKinney seconded the motion.

Mr. Rifkin said he believed RAC members were well-intentioned; they would not be part of the medical research community if they did not think they were trying to improve the lot and welfare of humanity. Mr. Rifkin said it is very difficult for any profession to critique itself. He asked the members of the committee to look at their world view before they made any "hasty" decision.

Mr. Rifkin suggested RAC members were affected by the views they held about modern science; he asked the members of RAC to look at those assumptions and consider that there are other people who do not share that world view.

Mr. Rifkin said the history of every technological revolution shows that every great technology brings both benefits and costs. The more powerful and impressive the technology, the better able to expropriate, secure, and use natural resources for human needs, the greater the potential costs that will be heaped on the ecosystem and paid by future generations. Mr. Rifkin thought it either naive or disingenuous to believe that there are no risks, no costs associated with the biotechnology revolution.

Mr. Rifkin reiterated his position that technologies mortgage the future to provide security for the present. He said:

"I think there are certain technologies that are so powerful inherent to the technological categories themselves that we have to ask the question, is it appropriate to use them."

Mr. Rifkin said Dr. Brinster's experiments are an attempt to develop super-animals, animals that would grow bigger and faster and provide commercial advantage in the market place. Mr. Rifkin contended that if this procedure becomes commercially feasible, livestock will be dramatically affected. The long-term implications are "model culturing" and the loss of gene diversity. "Model culturing" of animals will affect the well-being of society because society becomes more vulnerable to losses of these animals because the animals lack genetic diversity.

Mr. Rifkin said:

"There are specific parts of this genetic therapy that are more problematic than others but to suggest that at every juncture if we don't give the scientific community full license to pursue any kind of research in any area that we will be in some way condemning all present and future human beings on this planet to suffering, disease, death, that to me suggests a syndrome of fear and it needs to be addressed...."

Mr. Rifkin asked how RAC so "prematurely" reached the conclusion that the benefits in the long-run outweigh the risks; only a few experiments of this

type have been done. How can RAC be so convinced the long-term benefits outweigh the costs?

He suggested that:

> "...it would be very very foolhardy in a one hour discussion on crossing genetic lines for you to pass a resolution saying that you would encourage this from here henceforward. I think it's more responsible to put a moratorium on this research until such time as these questions are being properly addressed by the American public."

Mr. Rifkin thought the letters that had been received on this topic did not represent an accurate cross-section of the American public.

Dr. McKinney felt Mr. Rifkin had either misunderstood or misconstrued the comments of RAC members. Dr. McKinney did not think any member of RAC had suggested there are not problems associated with any area of research. However, the history of RAC has been an orderly process of consistently exercising care and prudence in approaching the utilization of recombinant DNA technology. Dr. McKinney thought Dr. Gottesman's motion was to continue this orderly process so the potential benefits of this technology might be assessed.

Mr. Mitchell pointed out that Mr. Rifkin's proposal would prohibit certain experimentation involving the transfer of genes; thus, the question before the RAC is whether this area of scientific research should be prohibited.

Dr. Rapp stressed that at least he and probably most RAC members had not spent "one hour" considering this issue. Most members have been thinking about these issues for a number of years. RAC members recognize there are risks associated with any new technology; however, a total prohibition will prevent society from ever learning whether these potential risks are real or mythical.

Dr. Rapp said in our lifetime smallpox virus has been wiped out; he did not think the world was poorer for this action. He thought the Brinster experiments had to be considered in the context of the overall pattern and overall benefits of genetic engineering. Dr. Rapp said some studies of gene regulation, translation, and expression have to be done in foreign hosts. Studies such as these are leading, hopefully, to a solution of problems such as cancer. Prohibiting these types of experiments would destroy efforts to study very major human disease syndromes. Dr. Clowes said there are a number of scientific developments in which the benefits enormously outweigh the costs.

Dr. Rapp said a total prohibition would stop a whole field of science in its tracks. Such attempts at prohibition have not worked at any time in history. RAC should continue to evaluate proposals; otherwise, researchers would perform these experiments in other parts of the world. Should this occur, the U.S. government would lose whatever control it now has over

these types of experiments. Dr. Rapp said he favored Dr. Gottesman's motion.

Dr. Holmes said Mr. Rifkin and the RAC do have differences in perspective; however, it's not that RAC only sees the benefits where Mr. Rifkin only sees the risks. The difference in world view is that seeing both the risks and benefits, Mr. Rifkin would prohibit seeking the benefits whereas the RAC would prefer to press on to try and maximize the benefits while minimizing the risks.

Dr. Joklik said many RAC members have thought about these types of problems for many years; the aim of biomedical research has been to make our children and our children's children healthier.

Dr. Joklik said a difficulty in communicating with Mr. Rifkin is that as soon as one of Mr. Rifkin's concerns is allayed, another concern surfaces. Dr. Joklik said Mr. Rifkin now asks how scientists can be sure this new technology will provide benefits for mankind. Recombinant DNA is the means for answering many questions. Ten years after the inception of this new technique, so much more about the workings of the human cell and the human organism is known, including a more detailed knowledge of the nature of human genetic material. In addition, we now have the ability to manipulate the genetic material. One simply has to ask oneself how much more will we know in another ten years, a very short time in the experience of mankind.

Dr. Joklik said Mr. Rifkin was attempting to arrest a process which has been spectacularly successful.

Dr. Walters asked Dr. Gottesman if she would accept a friendly amendment to her motion; he proposed to add to the motion the notion of protecting animal welfare as well as human welfare through a better understanding of animal diseases. Dr. Gottesman agreed to add such language to her motion. Dr. McKinney, the seconder of the motion, also agreed.

Dr. Landy said RAC is saying it is unconscionable to prohibit exploring this avenue of research. He asked Mr. Rifkin if there are any examples in history where a social problem has been successfully solved before the technology was developed to address the problem.

Mr. Rifkin said the Iroquois nation of North America had a civilized and advanced culture. These people followed a specific procedure whenever they considered some environmental, social, or cultural change. They asked in the deliberation process what effect the proposed change would have seven generations in the future. In some cases, the Iroquois decided the particular change would have more costs than benefits and decided not to implement it.

Mr. Rifkin said genetic engineering is one approach to the future; it is not the only approach. He emphasized that there are other approaches to solving problems. He offered as an example attempts to deal with heart

and lung diseases and cancer. He said these diseases have an environmental component as well as a genetic component. Mr. Rifkin said he would be thrilled if NIH money were spent studying how the environment triggers genetic diseases rather than on research on gene transfers.

Mr. Mitchell asked Dr. Bowman whether environmental factors are a cause of cystic fibrosis. Dr. Bowman said environmental factors are not a cause; cystic fibrosis is a genetic illness.

Dr. Gottesman said Mr. Rifkin's characterization of RAC's activities as always giving the go-ahead is untrue as RAC has often turned down requests to proceed. Dr. Gottesman asked Mr. Rifkin to be honest and accurate in his portrayal of RAC and RAC's activities, and of the question currently before RAC. In this instance, a single gene will be moved from one organism to another; all sheep are not about to be turned into giant sheep nor are people with bat wings going to be created.

Mr. Richard Pollack identified himself as having been associated for a two year period with Sandia Laboratories as a consultant to the Nuclear Regulatory Commission (NRC), as having served with the NRC on the Three Mile Island investigation, and as being "close" to Mr. Rifkin.

Mr. Pollack said Mr. Rifkin was asking:

> "...if the basic question of the environmental impact...has been ignored by this committee...What kind of road are we moving down? ...with such a powerful tool with such great consequences, not to have that kind of basic methodology to assure the public is very disconcerting, whether on a concrete issue or on a less abstract issue...."

Dr. Fox asked why others seem to think there is an ethical issue to be discussed. He said, "Surely there is not some dialectical tension here that cannot be reconciled, that somewhere between us is meaning and substance to the reality around us."

Dr. McKinney reminded the proponents of what their proposal entailed; a complete prohibition of certain types of research. He then called the question.

By a vote of nineteen in favor, two opposed, and one abstention, the RAC agreed to close debate.

Dr. Gottesman then repeated the language of her modified motion:

> "That RAC reject the amendments proposed by Mr. Rifkin and published in the Federal Register of September 20, 1984, Section II. Both the importance of this class of experiments in current scientific research and the long-term possibilities for treatment of human and animal disease and the development of more efficient food sources make it a moral imperative that we strongly oppose the blanket prohibition of this class of experiments."

By a vote of twenty-two in favor, none opposed, and no abstentions, the RAC approved Dr. Gottesman's motion.

Mr. Mitchell suggested that a document be prepared to set forth the statements and concerns of the RAC and others. Dr. Gottesman said the minutes of the RAC meeting could form the basis of that document.

IX. ADJOURMENT

The meeting adjourned at 3:01 p.m., Monday, October 29, 1984.

Respectfully submitted,

Elizabeth A. Milewski, Ph.D.
Rapporteur

William J. Gartland, Jr., Ph.D.
Executive Secretary

I hereby certify that, to the best of my knowledge, the foregoing Minutes and Attachment are accurate and complete.

Date

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DRAFT

POINTS TO CONSIDER IN THE DESIGN AND SUBMISSION OF HUMAN GENE THERAPY PROTOCOLS

WORKING GROUP ON HUMAN GENE THERAPY
RECOMBINANT DNA ADVISORY COMMITTEE

OUTLINE

Preamble

A. Focus on somatic-cell gene therapy

B. Guidance provided by general rules for research involving human subjects and President's Commission report on Splicing Life

C. Review procedures

D. Procedure for periodic revision of "Points to Consider"

I. Issues Covered by the Department of Health and Human Services (DHHS) Regulations for Research Involving Human Subjects

A. Research design, anticipated risks and benefits

1. Objectives and rationale

a. Disease to be treated
b. Natural history of disease
c. Alternative treatments

2. Research Methods

a. Structure of genetic material to be inserted
b. Tissue culture and animal studies

3. Clinical and public-health considerations in the treatment of patients

4. Qualifications of investigators, adequacy of laboratory and clinical facilities

B. Selection of subjects

C. Informed consent process

D. The protection of privacy and confidentiality

II. General Social Issues Not Covered by the DHHS Regulations for Research Involving Human Subjects

Example: What effect, if any, is the proposed somatic-cell therapy likely to have on the reproductive cells of treated patients? Please provide laboratory data or bibliographic references that pertain to the answering of this question.

III. Requested documentation

A. Original protocol or grant application

B. Responses to the "Points to Consider"

LeRoy Walters
10/25/84